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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,632	06/09/2000	Susan Lindquist	27373/34978A	2820

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/591,632	Lindquist et al.
Examiner	**Art Unit**
Michael Brannock	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 3, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *60, 61, 65, 67, 81, 101-114, and 116-143* is/are pending in the application.

4a) Of the above, claim(s) *60, 61, and 111-114* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *65, 67, 81, 101-110, 116, and 119-143* is/are rejected.

7) ☒ Claim(s) *117 and 118* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Claims 60, 61, 111-114 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14, 5/13/02.

Applicant is reminded that the claims are under examination only to the extent that they read on the elected invention, i.e. polypeptides having a reactive SCHAG amino acid sequence, comprising SEQ ID NO: 2 or a fragment thereof, a modified cysteine residue, and a metal atom substituent.

Response to Amendment

Claim Rejections - 35 USC § 102

2. Claims 65, 67, 101 stand rejected and new claims 119, 120, 139 and 141 are rejected under 35 U.S.C. 102(b) as being anticipated by Gregori et al., J. Biol. Chem. 272:1(58(62)1997, as set forth previously and reiterated below.

Gregori et al. disclose a polypeptide comprising a self-aggregation domain of Amyloid-β protein (residues 1-40, as is well known in the art) comprising the substitution of residue 40 with a cysteine residue having a reactable side chain and further modified with a metal ion (gold), see col 1 of page 59. Gregori et al. further disclose that the labeled peptide forms ordered aggregates

see col 1 of page 60, therefore one of ordinary skill in the art would expect that the gold labeled side chain is exposed to the environment in an ordered aggregate because the gold does not appear to inhibit aggregation as would be expected if the gold was buried in the interior of the aggregate.

Applicant argues that Gregori et al. failed to disclose that the labeled peptide formed ordered aggregates and contains teachings that suggest that it did not. Applicant argues that Figure 2 (presumably Applicant is referring to Fig 2A, lane 2) shows a single band of 17 kD that would indicate to the reader that no aggregation occurred such as would produce monomer and dimer bands. This argument has been fully considered but not deemed persuasive. This Figure shows that the gold labeled peptide migrates under these conditions as a complex with a higher molecular weight than the unlabeled monomer and dimer shown in lane 1. This is explicitly taught in the figure legend at line 13.

Applicant argues that the teachings in Col 1 on page 60 refer to amyloid/proteosome interactions, not self aggregation of the gold labeled amyloid protein and one would not expect self aggregation of the amyloid based on these conditions. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art appreciates that Col 1 of page 60 discusses the difficulties encountered during the study of the amyloid/proteosome interaction *because* of the inherent property of the gold labeled amyloid protein to self aggregate, see the first full paragraph of Col 1. The authors presume that the gold labeled amyloid protein has the same self-aggregating properties as the wild-type, thus giving rise to the difficulties in

analyzing the kinetics of amyloid/proteosome binding, i.e, because the gold labeled amyloid protein is self aggregating at higher concentrations, see also lines 17-22 of the last paragraph of Col 1. One skilled in the art would have no reason to doubt this presumption, absent evidence to the contrary. Thus, the skilled artisan would expect that the "higher ordered forms" of Aβ referred to by Gregori et al. in the first full paragraph of col 1 of page 60 would necessarily include "filamentous" and "fibrous" polymers required of new claims 120 and 139, based on the established nature of amyloid protein, absent evidence to the contrary.

Applicant argues that the exposure of the reactive cysteine is only inferred due to the presence of aggregates, yet no aggregates are disclosed. This argument has been fully considered but not deemed persuasive for the reasons above. It is noted that Applicant does not assert that the aggregates would not be expected to form nor that the reactive cysteine would not be expected to be exposed.

Applicant's arguments are persuasive regarding claim 116; it appears that this claim was erroneously included in the rejection.

3. Claims 81 stands rejected under 35 U.S.C. 102(b) as being anticipated by Paushkin et al., Science 277(381-383)1997, as set forth previously. The specification asserts that cysteine, lysine, tyrosine, glutamate, aspartate, and arginine possess reactable side chains (e.g. page 24) and that the NM fragment of yeast Sup35p has multiple cysteine, lysine, tyrosine, glutamate, aspartate, and/or arginine residues wherein the side chains are exposed to the environment and

could serve as reactive sites in ordered aggregates of the polypeptide, see Table at page 86 for example. Paushkin et al., disclose the NM fragment of yeast Sup35p, see Fig. 1, for example.

Applicant argues that the claims have been amended to require two selectively reactive side chains. And that one would not be motivated to make exactly two selectively reactive side chains. This argument has been fully considered but not deemed persuasive. The claims do not require that there be exactly two selectively reactive side chains. The polypeptide disclosed by Paushkin et al. has two reactive side chains; it has more than two, but it does have two.

4. The rejection of claims 65, 67, 81, 101 under 35 U.S.C. 102(b) as being anticipated by WO 96/28471, as set forth previously is withdrawn in view of Applicant's persuasive arguments.

Claim Rejections - 35 USC § 103

5. Claims 102-110 and 116 stand rejected and new claims 119-122, 124, 125, 126, 132, 134, 135, 137-140, 142, 143 are rejected under 35 U.S.C. 103(a) as being unpatentable over King et al. PNAS 94(6618-6622)1997 in view of Gregori et al., J. Biol. Chem. 272:1(58(62)1997, as set forth previously and recast in light of Applicant's amendments.

It is noted that in the previous Office action, the substituted amino acid taught by Gregori et al., was erroneously referred to as lysine in the last paragraph of the rejection. The substituted residue is cysteine (see Col 1 of Gregori et al.). This error does not appear to effect either the

merits of the rejection nor any aspect of the arguments presented. The rejection, including this correction, is repeated below.

King et al. teach that residues 2-114 of the yeast Sup35 protein constitute the prion aggregation domain (see the Title and Abstract) see the Abstract and page 6618 and col 2 of page 6621. King et al. also teach the use of a polyhistidine tag (page 6618) to purify the protein, as is old in the art. Further, the use of polyhistidine tags or epitope tags for protein purification is old and established in the art. King et al. teach methods of monitoring the ordered aggregation of prion-like proteins, e.g. Electron Microscopy, Circular Dichroism, Protease K resistance assay and seeding assay (see Experimental Procedures). King et al. do not disclose that the method of monitoring aggregate formation involve the use of a gold labeled polypeptide, wherein an amino acid exposed to the environment is substituted with an amino acid having a reactable side chain.

Gregori et al. disclose an improved method of monitoring prion-like aggregation with electron microscopy using a gold labeled substituted amino acid (see the Abstract). Gregori et al. disclose a polypeptide comprising a self-aggregation domain of Amyloid-β protein (residues 1-40) comprising the substitution of residue 40 with a cysteine residue having a reactable side chain and further modified with a metal ion (gold), see col 1 of page 59. Gregori et al. further disclose that the labeled peptide forms ordered aggregates see col 1 of page 60, therefore one of ordinary skill in the art would expect that the gold labeled side chain is exposed to the environment in an ordered aggregate because the gold does not appear to inhibit aggregation as would be expected if the gold was buried in the interior of the aggregate.

Additionally, new claim 140 requires that the fibrous polymer be attached to a solid support. The use of solid supports for the analysis of proteins is old and established in the art, e.g. both Gregori et al. and King et al. attach the proteins to solid supports, i.e. for use in electron microscopy and western blotting, see col 1 of pg 59 of Gregori and col 2 pg 6618 of King.

Therefore, it would be obvious to one of ordinary skill in the art, with reasonable expectation of success, at the time the invention was made, to substitute an amino acid bearing a side chain exposed to the environment (i.e. an amino acid wherein substitution of which would not disrupt aggregate formation) with a cysteine residue and to label the cysteine residue with a gold ion for use in electron microscopic investigation of prion-like aggregate formation as taught by Gregori et al. when practicing the method of monitoring the prion-like aggregate formation of the Sup35 protein as taught by King et al.. The motivation to do so is provided by King et al. who demonstrate the importance of monitoring prion-like aggregate formation of the Sup35 protein.

Applicant argues, essentially, that the abundance of methods available for monitoring prion aggregation would have dissuaded King from using any other methods. This argument has been fully considered but not deemed persuasive. Gregori et al. disclose an improvement over the method used by King, e.g., Gregori discloses an improvement in the method of electron microscopy.

Applicant's arguments as to whether or not Gregori teach that the protein self-aggregates have been substantially addressed previously. One of ordinary skill in the art would appreciate

that the self-aggregating property of the protein is obvious from the teachings of Gregori at col 1 of page 60. It is true that the scientific focus of Gregori et al. is concerned with the aggregation of the amyloid protein and the proteosome, however, one of ordinary skill appreciates that the technique of modifying the amyloid protein with gold improves the study of any aggregates that the protein may form. It is King et al. that provide the motivation to study self aggregation, additionally, this motivation is pervasive and is old and well established in the art of amyloid and prion aggregate formation.

Applicant argues that one would not have been motivated to change an amino acid at the C-terminal of a peptide when studying self aggregation. This argument has been fully considered but not deemed persuasive. Gregori et al., demonstrate self aggregation of the c-terminally modified peptide in Figure 2, lane 2, and also state that the modified peptide exhibits self aggregation properties similar to the native peptide which interfere with the analysis of the kinetics of its interaction with the proteosome (see the last paragraph of pg 60 col 1). Thus one of ordinary skill in the art would be motivated to modify the peptide at the C-terminal as Gregori did to study self aggregation.

6. Claims 65, 67, 81 and 101 stand rejected and new claims 119, 120, 139-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5750361 in view of Stayton et al. J. Biol. Chem. 263(27)1344-13548, 1988, as set forth previously and recast below in view of Applicant's amendments.

U.S. Patent No: 5750361 discloses methods of assaying formation of prion complexes (i.e. SCHAG amino acid sequences) by constructing polypeptides comprising prion aggregation domains labeled using materials and methods well known in the art including florescent dye and spectrophotometrically-detectable chromophores (see col 11 bridging col 12). U.S. Patent No: 5750361 discloses assays to determine that the labeling occurs at positions exposed to the environment, i.e. that the label does not interfere with complex formation (e.g col 11 and 12). U.S. Patent No: 5750361 does not specifically recite that the act of labeling the polypeptide include the steps of choosing an amino acid residue in the sequence having a side chain that is exposed to the environment and substituting this amino acid with one having a reactive side chain; however these steps are old and well established to in the art of protein complex detection. For example, Stayton et al. disclose a method of labeling a polypeptide comprising identifying residues having side chains exposed to the environment (Threonine at positions 6 and 68 of Cytochrome b5) and substituting these residues with residues having a reactive side-chain and further modifying the reactive side chains with a fluorescent agent (see the Abstract and col 2 of page 13544). U.S. Patent No: 5750361 also disclose that the polypeptides can be further modified to accept a biotin group through methods well known in the art, e.g. derivation of a reactive lysine side chain (see col 12, L27-39).

Additionally, new claim 140 requires that the fibrous polymer be attached to a solid support. U.S. Patent No: 5750361 discloses that the modified peptides be attached to a solid support, e.g. col 11, lines 48-50.

Therefore, it would have been obvious to one of ordinary skill in the art, with reasonable expectation of success, to produce a polypeptide comprising a prion aggregation domain for use in an assay to detect prion aggregates (and thus producing the aggregates themselves) labeled with a fluorescent or other spectrophotometrically-detectable substituent, and also a lysine residue for biotinylation, as taught by U.S. Patent No: 5750361 and to accomplish this by selecting a residue having a side chain exposed to the environment and replacing that residue with one having a reactable side chain and then further modifying the side chain with a fluorescent dye, as taught by Stayton et al. and/or a biotin molecule as is old in the art. The motivation to do so was provided by U.S. Patent No: 5750361 wherein it is stated that the polypeptide should be modified as described in the art and that amino acids could be substituted as long as the change does not effect complex formation (col 7, L30-36) and by Stayton et al who provide methods of labeling a polypeptide, wherein the labeled polypeptide is useful for detection of complex formation.

Applicant argues that one would not be motivated to look for additional methods to monitor the aggregation domain of prion proteins. This argument has been fully considered but not deemed persuasive. The rejection is not based on a motivation to provide a different method to measure prion aggregation. These methods are fully disclosed by Prusiner. Rather, in following the methods taught by Prusiner, the artisan would be motivated to make the claimed product. Prusiner teach that, for the purpose of monitoring peptide interactions, the peptides should be labeled using methods known in the art (e.g. col 11 bridging 12). Substituting amino

acids with amino acids having reactable side chains for the purpose of attaching labels to the protein to monitor protein interactions is old and well established in the art, e.g. Stayton et al. is cited as evidence that such techniques were well known in the art.

Applicant argues that Stayton et al. relies on an entirely different field and entirely different problem. This argument has been fully considered but not deemed persuasive. First, the examiner disagrees with Applicant's narrow characterization of the field of protein interactions. The examiner can find no reference in either the instant specification nor the prior art that would suggest that labeling techniques that are appropriate to the study of cytochrome proteins and to the study of heterologous protein interactions would not be appropriate for the study of homologous interactions among prions. Further, Stayton is being relied upon to provide evidence that the technique of labeling a peptide by substituting with a residue having a reactive side chain, for the purpose of examining protein interactions, was well known in the art at the time of filing of the Prusiner patent and would therefore be encompassed by Prusiners teachings regarding labeling.

Applicant argues that the Prusiner patent is primarily concerned with the inhibition of complex formation in naturally occurring disease promoting proteins and, thus would not be motivated to make the required amino acid substitutions. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art appreciates that most of techniques for labeling recited by the Prusiner patent (e.g. at col 11 bridging 12) involve the of chemical substituents to the native protein- thus changing the chemical properties of the

native amino acid that the substituent is attached to. Each of the labeling methods have their own advantages and disadvantages, as is old and well established in the art; the advantage of selectively adding a reactive side chain lies in the ability to determine where the chemical label will be put (e.g. as taught by Stayton et al.). Pursiner contemplated the desirability of making amino acid sequence variants of native amino acid sequences, e.g. col 11, line 32, and provided the additional teaching that such variants need to be screened for aggregate forming ability (col 7, L30-36). Thus, the artisan would not be dissuaded from making such changes when adding labels such as florescent dyes or spectrophotometrically-detectable chromophores (as taught by Prusiner). To the contrary, the artisan of ordinary skill understands that the very act of adding a label to a particular residue changes the chemical nature of that residue (much like amino acid substitution would), yet by controlling which residues are labeled (through amino acid substitution) labels can be introduced at locations on the peptide that have less of a negative effect on the natural binding properties of the peptide (e.g. as taught by Stayton et al.). These concepts are old and well established in the art.

Applicant argues that no reasons have been presented as to why the artisan would be motivated to modify a protein with two different, and thus selectively reactable amino acids, as is required by claim 81. This argument has been fully considered but not deemed persuasive. The basis of the rejection clearly pointed out the motivation to make two selectively reactable side chains, see the last paragraph of the previous rejection and above.

Applicant argues that the polymer of claim 67, which does not include a label, would not have been obvious from the cited references. This argument has been fully considered but not deemed persuasive. Pursiner teach that amino acid sequence variants, once made, must be assayed for aggregate formation (col 7, line 36); this would be obvious to anyone of ordinary skill in the art. Thus, the artisan, being a laboratory scientist, would certainly be motivated to make the variant and then test it for aggregation with and without the label to determine the effect, if any, of the mutation and of the label; these procedures for establishing experimental controls are standard and well established, as also evidenced by Stayton who determined the effect of the label by comparing the properties of the labeled and unlabeled mutants, see for example, page 13545: Florescent Labeling of Cytochrome b.

7. Claims 102-109 and 116 stand rejected and new claims 121-126 and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5750361 in view of Stayton et al. J. Biol. Chem. 263(27)1344-13548, 1988 and in further view of King et al. PNAS 94(6618-6622)1997, as set forth previously and reiterated below.

Claims 102-109, 116, 121-126 require the elements of claims 65, 67, 81, 101, 119, 120, 139-141 as discussed above, yet claims 102-109 and 116 also require the aggregation domain be that comprising residues 2-113 of the yeast Sup35p and also a epitope or poly histidine tag. King et al. teach that residues 2-114 of the yeast Sup35 protein constitute the prion aggregation domain (see the Title and Abstract) and are analogous to the amyloid aggregation domains (referred to in

the U.S. Patent No: 5750361), see the Abstract and page 6618 and col 2 of page 6621, as is well established in the art. King et al. also teach the use of a polyhistidine tag (page 6618) to purify the protein, as is old in the art. Further, the use of polyhistidine tags or epitope tags for protein purification is old and established in the art. U.S. Patent No: 5750361 further teach the use of epitopes (i.e. epitope tags) to monitor the aggregate forming properties of the polypeptides (see col 9, L52 to col 10, L12).

Therefore, it would have been obvious to one of ordinary skill in the art, with reasonable expectation of success, to produce a polypeptide comprising a prion aggregation domain comprising residues 2-113 the yeast Sup35p, as taught by King et al. for use in an assay to detect prion aggregates as taught by both U.S. Patent No: 5750361 and by, King et al, labeled with a fluorescent or other spectrophotometrically-detectable substituent, and also a lysine residue for biotinylation, as taught by Stayton et al., wherein the reactive side chains are introduced by amino acid substitution as taught by Stayton et al. It would also be obvious to further monitor the aggregation of the polypeptides using epitope tags, as taught by Stayton et al. The motivation to do so was provided by both King et al. and U.S. Patent No: 5750361 wherein the importance of monitoring the prion-like aggregation of polypeptides is particularly pointed out (see the Abstracts of both King et al. and U.S. Patent No: 5750361).

Applicant's arguments regarding U.S. Patent No: 5750361 and Stayton et al. have been discussed above and are not persuasive. Additionally, Applicant argues that there would be no motivation for substituting the yeast sequences of King for the mammalian PrP prion sequences

of the Prusiner patent. This argument has been fully considered but not deemed persuasive. As set forth above the motivation was provided by both King et al. and U.S. Patent No: 5750361 wherein the importance of monitoring the prion-like aggregation of polypeptides is particularly pointed out (see the Abstracts of both King et al. and U.S. Patent No: 5750361) as well as the desire to find mechanisms common to both mammalian and yeast prion assembly, see the last paragraph of King et al.

New Rejections:

8. Claims 127-131 and 133-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5750361 in view of Stayton et al. J. Biol. Chem. 263(27)1344-13548, 1988 and King et al. PNAS 94(6618-6622)1997 as set forth above regarding claims 102-109, 116, 121-126, and in further view of Paushkin et al., Science 277(381-383)1997.

New claims 127-131 and 133-138 require the elements of claims 102-109, 116, 121-126 as discussed above, yet new claims 127-131 and 133-138 also require that the fragment of the claimed peptide comprise residues 2-253 of SEQ ID NO: 2, i.e. the NM fragment (see pg 10). Paushkin et al., disclose the NM fragment of yeast Sup35p and teach that it also retains prion aggregating properties, and is particularly useful for initiating and monitoring the aggregation process, see col 2 of page 382. Additionally, the physical properties required of the claimed proteins in claims 130 and 131 would be expected to be inherent properties of a protein showing

similar aggregate forming properties as the wild-type, as is taught to be preferred in U.S. Patent No: 5750361, e.g. at col 7.

Therefore, it would have been obvious to one of ordinary skill in the art, with reasonable expectation of success, to produce a polypeptide comprising a prion aggregation domain from yeast, as taught by King et al, comprising residues 2-253 the yeast Sup35p, as taught by Paushkin et al. for use in an assay to detect prion aggregates as taught by each of U.S. Patent No: 5750361, King et al, and Paushkin et al., labeled with a fluorescent or other spectrophotometrically-detectable substituent, and also a lysine residue for biotinylation, as taught by Stayton et al., wherein the reactive side chains are introduced by amino acid substitution as taught by Stayton et al. It would also be obvious to further monitor the aggregation of the polypeptides using epitope tags, as taught by Stayton et al. The motivation to do so was provided by Paushkin et al. who demonstrate that the NM fragment of yeast Sup35p retains prion aggregating properties, and is particularly useful for initiating and monitoring the aggregation process, see col 2 of page 382.

Claim Rejections - 35 USC § 112

9.The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 131 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is written such that it depends from itself. This appears to be a typographical error. For the purpose of this examination, claim 131 will be assumed to depend from claim 127.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 124, 127-131, 134-137 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a polypeptide of SEQ ID NO: 2, yet the claims require an essentially limitless number polypeptides having only 90% identity with SEQ ID NO: 2, e.g. sequences from other species, artificially mutated sequences and allelic variants. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that many of these proteins would work as required by the claims, one would not be able make useful predictions as to the amino acid positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polypeptide, that of the naturally occurring SEQ ID NO: 2, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 2, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

Thus, with the exception of the of the polypeptide of SEQ ID NO: 2, the skilled artisan cannot envision encompassed variants. Therefore, only a polypeptide of SEQ ID NO: 2, and polypeptides *consisting* of fragments thereof, or polypeptides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Conclusion

13. Claims 117 and 118 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. This application contains claims drawn to an invention nonelected with traverse in Paper No. 14. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m.

The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

April 20, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600